IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Log-transformed data was submitted for analysis.

Results

Table 3. Naproxen mean plasma levels (+sd) for the subjects that received the test and reference formulations after an overnight fast.

TREATMENT A Reference			TREATMENT B Test		
Time(hrs)	Mean	CV%	Mean	CV%	P-Value
0	0.00	0.00	0.00	0.00	---
0.33	36.65	48.6	36.5	38.8	NS
0.67	69.6	18.2	69.99	13.6	NS
1	70.03	16.2	68.10	13.1	NS
1.33	65.77	12.1	64.73	12.7	NS
1.67	61.36	11.6	61.25	11.6	NS
2.00	57.29	12.9	57.35	9.6	NS
2.5	52.50	9.7	55.13	10.9	NS
3	49.96	11.7	49.80	12.0	NS
4	45.9	10.6	44.31	12.3	NS
6	37.10	14.2	37.28	9.5	NS
8	31.19	14.9	30.62	12.9	NS
12	23.32	14.5	22.09	17.6	NS
24	14.48	19.4	14.75	22.2	NS
36	8.37	26.7	8.59	27.6	NS
48	5.23	32.8	5.29	32.4	NS
60	3.29	39.2	3.24	35.9	NS

NS = Not significant at the p = 0.05 level.

Table 4. Mean pharmacokinetic parameters and % CV for subjects that received either the test or reference naproxen formulations following an overnight fast.

TREATMENT					
Variable	A=REF	B=Sidmak	Ratio (B/A)	N	Confidence Interval
AUCL[2] (μg/mlxhr)	961.62±15.0	969.99±14.0	1.008	24	98.9 to 103%
LNAUCL[4]	6.857	6.866	1.01	24	98.9 to 103%
AUCI[3] (μg/mlxhr)	1041.57±16.8	1056.75±16.4	1.01	24	99.5 to 103%
LNAUCI[4]	6.934	6.948	1.01	24	99.5 to 103%
CPEAK (μg/ml)	73.36 ± 11.8	76.77 ± 11.3	1.04	24	100 to 109%
LNCPEAK[4]	4.288	4.334	1.04	24	100 to 109%
KEL-1 (hr)	0.043±13.2	0.042±19.2		24	
HALF (hr)	16.11	16.39		24	
TPEAK (hr)	0.88	0.95		24	---

Observed Mean ± CV%

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 - infinity)
[4]Log Transformed(LNAUCL, Cmax)

Adverse Effects

Most adverse effects were observed for the test product and are summarized in table 6.

Subject Drop outs

The study began with 26 volunteers. Subject 18 withdrew for personal reasons prior to period 2 while subject 26 was discontinued due to non compliance.

Sample reassays:

2 samples out of 813 or 0.2% were reassayed.

Post-Prandial Study

Objective:

The aim of this study is to compare the oral absorption of naproxen tablets manufactured by Sidmak Pharmaceuticals with a commercial lot of the reference product, Anaprox tablets manufactured by Syntex following a single 550 mg dose.

Methods:

The study was conducted by (b)4 - Confidential Business under the direction of (b)4 - Confidential Business Samples were analyzed by (b)4 - Confidential Business Ph

I. Characterization of Study Group:

A. Inclusion criteria:

1. All volunteers selected for this study were male volunteers between the ages of 18 and 45 years. Weight range of the volunteers was within 10% of normal body weight relative to height and frame size.

2. Each volunteer was given a general physical examination within 30 days of initiation of the study. Each examination included blood pressure, general observations, history, complete hemogram (hemoglobin, hematocrit, WBC, differential), urinalysis (including microscopic), biochemistry (blood urea nitrogen, serum bilirubin [total]), HIV antibody screen. Volunteers selected for the study had no clinically significant abnormal findings.

3. Normal electrocardiogram.

B. Exclusion Criteria:

1. Volunteers with a history of alcohol or drug addiction during the past two years, gastrointestinal, renal, hepatic or cardiovascular disease, tuberculosis, epilepsy, asthma.

2. Any noted EKG abnormality.

3. History of adverse reactions or allergy to aspirin naproxen sodium, or other NSAID's.

4. Participation in a previous clinical trial or the donation of one pint or more of blood within the past 90 days.

5. Use of any OTC medication on a regular basis.

6. Positive screen for drugs of abuse.

7. Positive HBsAg or HIV screen.

8. Subjects that smoke.

C. Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was done in 12, healthy males.

A. Subjects fasted overnight and exactly 20 minutes before their dosing times they received a standard breakfast of:

1 English Muffin
1 Fried Egg
1 Slice of American Cheese
1 rasher of Canadian Bacon
Hashed Brown Potatoes
180 ml of orange juice
240 ml of milk

B. The products to be employed in the study were:

1. Test: Sidmak Pharmaceutical 550 mg naproxen tablet, Lot # 91-025 T, Lot Size [redacted](b)4 - [redacted]ablets.

2. Reference product: Syntex 550 mg Anaproxen tablet, Lot #53534, expiration date 1/94.

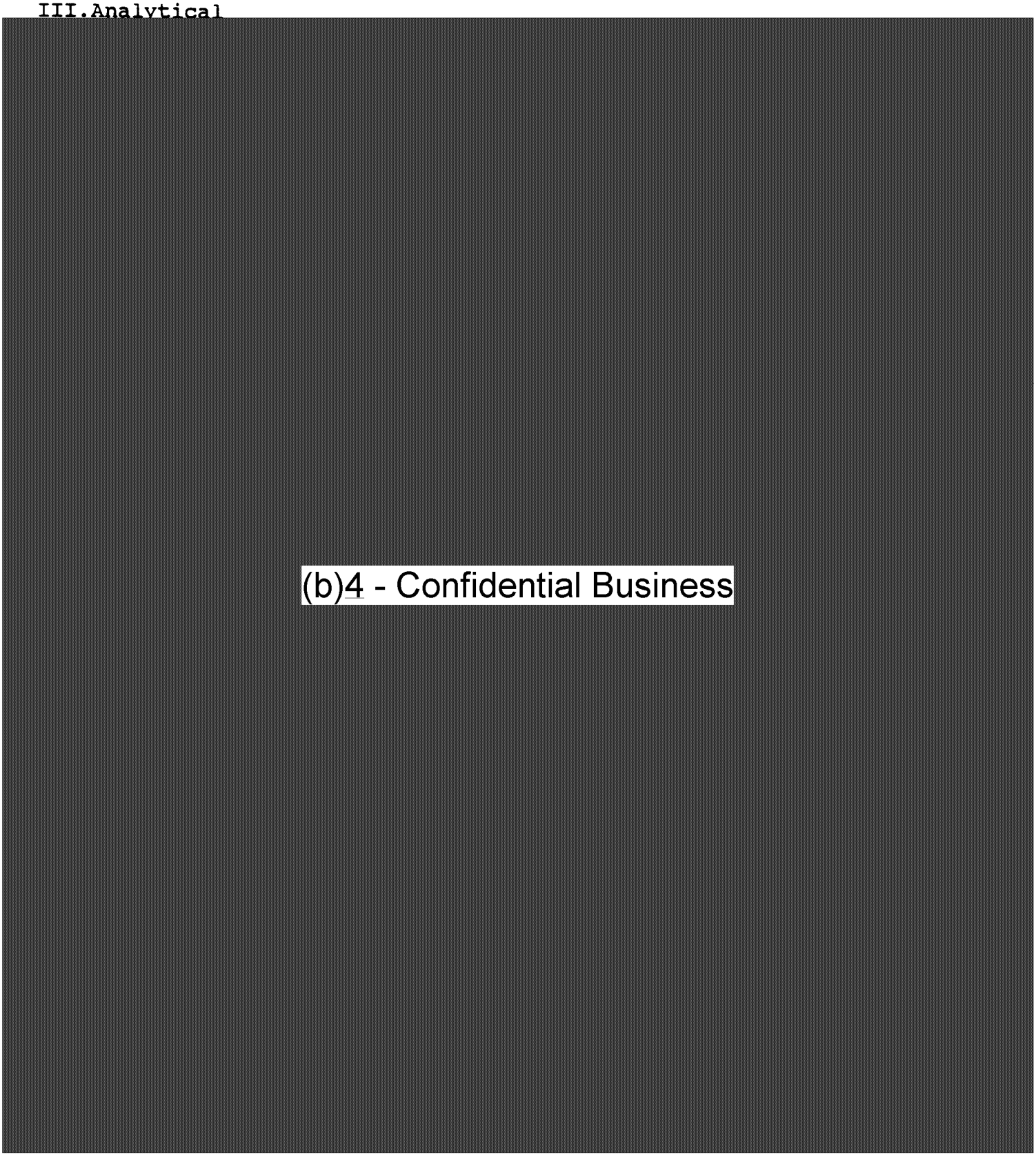
There was a 14 day washout between doses.

C. A 550 mg dose (1 x 550 mg) of each product (test and reference) was administered at time zero with 240 ml of water.

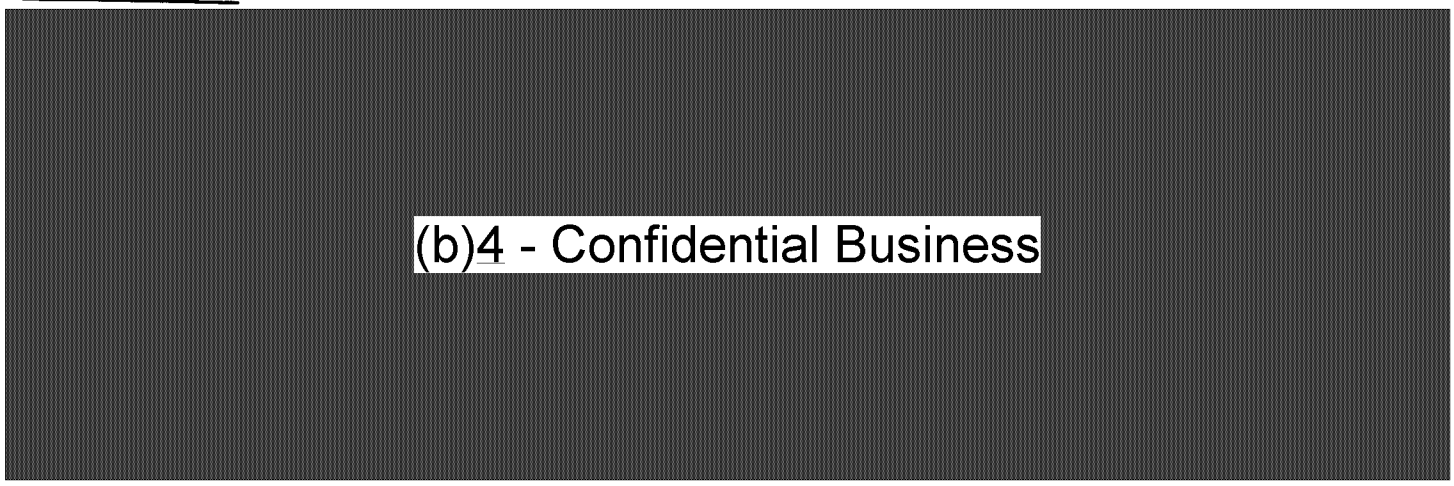
D. Plasma was collected pre-dose and at the following times post-dose: 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 60 hours.

E. During the study subjects were monitored for adverse reactions.

III.Analytical



Freeze Thaw



IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Log-transformed data was submitted for analysis.

Results

Table 7. Naproxen mean plasma levels (cv%) for the subjects that received the test and reference formulations after a high fat meal.

Reference-Syntex			Test-Sidmak	
Time(hrs)	Mean	CV%	Mean	CV%
0	0.00	0.00	0.00	0.00
0.33	4.86	108.8	3.67	103.5
0.67	19.71	88.1	16.89	70.7
1	36.62	68.8	39.16	51.4
1.33	51.24	32.2	47.91	39.0
1.67	56.04	24.4	52.14	33.9
2.00	61.29	24.9	55.74	28.7
2.5	60.6	15.3	52.91	24.3
3	54.13	14.6	50.25	19.3
4	49.38	18.8	47.1	18
6	37.07	18.0	37.77	14
8	30.99	14.4	29.89	21.1
12	22.18	22.7	23.57	20.3
24	12.39	21.7	13.06	26.1
36	6.88	32.1	7.18	21.8
48	4.22	34.6	4.08	24.7
60	2.45	52.4	2.17	56.4

Table 8. Mean pharmacokinetic parameters and % CV for subjects that received either the test or reference naproxen formulations following a high fat meal.

TREATMENT			
Variable	A=REF	B=Sidmak	% Diff.
AUCL[2] (μg/mlxhr)	865.41±15.3	866.63±14.0	0.1
AUCI[3] (μg/mlxhr)	937.27±17.0	927.12±14.5	1.01
CPEAK (μg/ml)	69.99 ± 16.9	64.23 ± 10.8	8.2
KEL-1 (hr)	0.044±19.8	0.047±10.3	
HALF (hr)	15.92	14.74	
TPEAK (hr)	1.88	1.93	

Observed Mean ± CV%

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 - infinity)

Adverse Effects

Most adverse effects were observed for the test product and are summarized in table 9.(See attached)

Subject Drop outs

The study began with 14 volunteers. Subject 7 withdrew because of a broken hand and the data was only analyzed for 12 subjects.

Sample Repeats:

2.5% or 10/398 samples were reanalyzed.

Comments:

1. The 90% confidence intervals for the fasting study are within the acceptable range of 80-120% of the reference.

2. The pharmacokinetic parameters from the post-prandial study are within 20% of those for the reference product.

3. The dissolution data for the 275 mg and 550 mg tablets is acceptable.

4. The 275 mg tablet is compositionally proportional to the 550 mg tablet that underwent bioavailability testing (table 10). However, the waiver for the 275 mg tablet can not be granted until the bioequivalence study for the 550 mg tablet is found to be acceptable.

Table 10. COMPOSITION OF THE 275 MG NAPROXEN TABLET

INGREDIENTS	MG/UNIT	%/UNIT
Naproxen Sodium, (Anhydrous) USP	275.0	69.42
Microcrystalline cellulose, NF (b)4 -	(b)4 - Confidential Business	
Povidone, USP (b)4 - Confidential		
*Purified water, USP		
Talc, USP #140		
Magnesium stearate, NF		
Opadry light (b)4 -		
Opadry clear, Confidential		
Purified water, USP		
Carnauba wax, NF powder		
Theoretical total weight of tablet in mg	396.15	100%

Deficiencies:

1. The firm did not give the name of the internal standard used in the assay.

2. The potency of Lot# 91-025T was not supplied by the firm.

3. The firm did not supply the zero time values to compare with their "comparison and stability" samples for their freeze thaw and other stability investigations.

Recommendation

1. The bioequivalence study conducted by Sidmak Pharmaceutical on its 550 mg naproxen tablet, lot 91-025T, comparing it to Syntex's Anaprox 550 mg tablet has been found to be incomplete by the Division of Bioequivalence.

2. The in vitro dissolution testing conducted on the 550 mg strength (lot # 91-025T) is acceptable.

3. The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of pH 7.4 phosphate buffer at 37 C using USP apparatus II paddle at 50 rpm. The test product should meet the following specifications:

Not less than (b)4 of the labelled amount of the drug in the dosage form is dissolved in 45 minutes.

/S/

Andre J. Jackson
Division of Bioequivalence
Review Branch I

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Concur: ate: 3/8/94

Rabindra Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence

cc: ANDA 74-242 original, HFD-630, HFD-600 (OGD, Hare), HFD-652 (Jackson, Wu), Drug File.

AJJ/041993/ntp/042393/122793/021894/WP #74358SD.N93

Table 9 . In Vitro Dissolution Testing

Drug (Generic Name):Naproxen
Dose Strength:550 mg
ANDA No.:74-242
Firm:Sidmak Pharmaceutical
Submission Date:July 2, 1992
File Name:74242SDW.792

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: 0.1M Phosphate BufferpH 7.4 Volume:900 ml
Specifications: (b)4 in 45 min
Reference Drug: Anaprox
Assay Methodology (b)4

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 91-025T Strength(mg) 550			Reference Product Lot # 53534 Strength(mg) 550		
	Mean %	Range	%CV	Mean %	Range	%CV
15	72.9	(b)4 -	8.5	70.0	(b)4 -	13.3
30	96.6	Confidential	2.9	95.2	onfidenti	5.4
45	99.6	Business	1.7	98.3	Business	4.6

USP XXII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: 0.1M Phosphate Bufferp H 7.4 Volume:900 ml
Specifications: (b)4 in 45 min
Reference Drug: Anaprox
Assay Methodology: (b)4

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 91-027T Strength(mg) 275			Reference Product Lot # 63315 Strength(mg) 275		
	Mean %	Range	%CV	Mean %	Range	%CV
15	81.6	(b)4 -	11.3	63.7	(b)4 -	9.4
30	97.9	Confidentia	5.4	93.2	onfidenti	3.2
45	100.7	Business	3.9	99.1	Business	2.1